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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/060,188	04/14/1998	DOMINIC P. BEHAN	AREN-001CIP(001.US2.CIP)	9333

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BOZICEVIC, FIELD & FRANCIS LLP
(ARENA PHARMACEUTICALS, INC.)
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/060,188	BEHAN ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,45-52,61,62,69,77,79 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,45-52,61,62,69,77,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *34,45-52,61,62,69,77,79 and 80* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submissions filed on 11/13/07 and 1/30/08 have been entered.

Status of Application, Amendments and/or Claims

Prior to entry of the two amendments, claims 34, 40, 45-66 and 69-74 were pending (including withdrawn claims 71-74); claims 1-33, 35-39, 41-44, 67, 68, 75 and 76 had been previously canceled.

(1) The amendment of 11/13/07 has been entered in full. Claim 59 is amended. New claims 77-79 are added.

(2) The supplemental amendment of 1/30/08 has been entered in full. Claims 40, 53-60, 63-66, 70-74 and 78 are canceled. Claims 34, 45, 52, 69, 77 and 79 are amended. New claim 80 is added.

Claims 34, 45-52, 61, 62, 69, 77, 79 and 80 are under consideration.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (6/13/07).

All rejections of claims 40, 53-60, 63-66 and 70 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 34, 45-52, 61 and 62 under 35 U.S.C. § 112, first paragraph at pg 7-10 for failing to comply with the written description requirement is *withdrawn* in view of Applicants' amendments to independent claim 69 that remove the limitation that "said endogenous GPCR has been associated with a disease or disorder in a mammal".

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 101, utility

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 34, 45-52, 61, 62, 69, 77, 79 and 80 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. This rejection was set forth previously and maintained at pg 3-6 of the 6/13/07 Office Action for claims 34, 45-52, 61, 62 and 69; new claims 77, 79 and 80 are herewith included in this rejection.

The rejection is first restated in view of Applicants' amendments to the claims, and then Applicants' arguments are addressed.

Independent claim 69 has been amended such that the endogenous G-protein coupled receptor (GPCR) used in the method is no longer limited to one "wherein said endogenous orphan has been associated with a disease or disorder in a mammal". Thus, the claim now encompass a method of using any endogenous GPCR "wherein an endogenous ligand for said endogenous GPCR has not been identified"; that is, a method of using any endogenous "orphan" GPCR. Furthermore, new independent claim 77 also encompasses a method of screening using of any "endogenous orphan GPCR".

As set forth in MPEP 2107, a ""specific utility" is *specific* to the subject matter claimed and can "provide a well-defined and particular benefit to the public" [citing *In re Fisher*]…This contrasts with a *general* utility that would be applicable to the broad class of the invention. Office personal should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating specified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound (citing *In re Kirk* and *In re Joly*)…Contrast the situation where an applicants

discloses a specific biological activity and reasonably correlates that activity to a disease condition". Furthermore, MPEP 2017 states, "Thus, a "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use are not substantial utilities…the following are examples of situations that require or constitute carrying out further research to identify or confirm a “real world” context of use and, therefore, do not define “substantial utilities”: A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved. B. A method of treating an *unspecified* disease or condition. C. A method of assaying for or identifying a material that itself has no “specific and/or substantial utility”…” (pg 6).

In the case *In re Fisher* (76 USPQ2d 1225 (CA FC 2005)) the U.S. Court of Appeals Federal Circuit stated, “Patent application does not satisfy utility requirement of 35 U.S.C. §101 unless it discloses both “substantial” utility for claimed invention, in form of significant and presently available benefit to public, as well as “specific” utility, which is well-defined and particular benefit to public” (pg 1225) and “an application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the “substantial” utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public” (pg 1230).

In the instant case, the claimed methods lack a specific and substantial utility because there is no specific and substantial utility for a non-endogenous compound modulatory compound identified by the claimed methods. With the exception of GPR3 (also known as ACCA), each orphan GPCR described in the specification lacks a specific and substantial utility. Furthermore, identification of a non-endogenous compound that can stimulate (i.e., agonize) or inhibit (i.e., antagonize) the activity of an orphan receptor does not provide a specific and substantial utility for such an identified compound. The specification teaches that such compounds may prove useful without identifying a specific use for the stimulation or inhibition of particular orphan GPCRs. The specification does not provide a reasonable correlation between the activity of any

of the orphan GPCRs and a specific and substantial use (e.g., treatment of a disease associated with the activity of the GPCR).

In the previous Office Action (6/13/07; pg 8), it was considered that the specification describes that the expression of GPR3, an orphan GPCR, is associated with epilepsy. The specification teaches, "GPR3 is expressed in much higher levels in human epilepsy tissue samples (tissue source: temporal cortex), as compared with controls, as evidenced by RT-PCR analysis (Figure 15)" (pg 75). However, the association of GPR3 with a specific disease (epilepsy) does not provide a specific and substantial utility for the claimed method even as practiced with GPR3. While measurement of increased GPR3 expression could possibly be used to confirm a diagnosis of epilepsy, this finding does not provide a use for agonists or antagonists of GPR3 identified by the claimed methods. The overexpression of GPCR in tissue from a person with a particular disease does not reasonably indicate that increased activity of said GPCR is a cause of the disease rather than a consequence. For example, with respect GPCR perturbations in the disease hypertension, "it has been difficult to determine whether they are the cause or consequence of the disease" (Feldman, 2002. Molecular Pharmacology. 61(4): 707-709). With respect to temporal lobe epilepsy, Janigro (2008. Epilepsy Currents 8(1): 23-24) teaches that "[a]s with many pathological findings in neurodegenerative diseases, it is difficult to determine if the changes are a cause or consequence of epileptic seizures" (pg 23). As such, at the time of filing it would require further research for the skilled artisan to confirm that increased GPR3 activity plays a role in epilepsy, such that administration of an antagonist could be used to treat epilepsy. Thus, it would require further research for the skilled artisan to identify or confirm a “real world” context of use for the agonists and antagonists of GPR3 identified by the claimed methods.

In summary, the proposed uses of the claimed invention to identify non-endogenous compounds that modulate the activity of orphan GPCRs requires further research to identify a specific and substantial use for the identified compound. Therefore, the application fails to provide guidance as to how one of skill in the art could use the claimed method in a way that constitutes a specific and substantial utility.

Applicants' arguments (11/13/07; pg 7-9 and 1/30/08; pg 6-8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the 11/13/07 response, Applicants argue that the claimed method will work with any orphan GPCR and thus "are not, and should not be, limited to any particular orphan receptor. Because the claims are not limited to a particular orphan receptor, they are likewise not limited to a particular disease or disorder" (pg 7). Applicants further argue that the claims are directed to a "research tool" that "plays an important role in developing a biopharmaceutical end product (compounds)". Applicants argue that the claimed method provide a novel means for identifying modulating compounds of orphan receptors, which at the time of filing, "were not screened until they had been "de-orphanized" (i.e., an endogenous ligand had been identified)", which is a "very expensive, time-consuming and oftentimes unsuccessful" process.

Applicants' arguments have been fully considered but are not found persuasive. The claims have not been rejected because they are not limited to any particular orphan GPCR. Instead, the claims are rejected because they are directed solely to a method of identifying compounds for which there is no specific and substantial utility once identified. This is because the compounds modulate the activity of uncharacterized orphan receptors and this activity has not been associated with any particular, immediate use. With respect to "research tools", MPEP 2107 cautions that " [l]abels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention" and "Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm". As set forth in the above rejection, in the instant case further research would be required to identify a specific and substantial use for modulating compounds identified by the claimed method. Furthermore, the benefits with regard to expense, time and success of identifying non-endogenous

modulating compounds of orphan receptors does not obviate the requirement for a specific and substantial use for the compounds once identified.

In both the 11/13/07 response (pg 8-9) and the 1/30/08 response (pg 7), Applicants argue that the "real world" utility and significance of the claimed invention is appreciated by investors and biotechnology companies. In support, Applicants point to two press releases from the assignee Arena Pharmaceutical, released 2/22/99 (Exhibit A submitted with the 11/13/07 response) and 11/15/99 (Exhibit B submitted with the 11/13/07 response).

Applicants' arguments have been fully considered but are not found persuasive. Patentable utility is not measured by commercial viability. A discovery or idea may generate commercial interest simply in hopes that after further research is performed a specific and substantial utility may be identified. Applicants' claimed methods are analogous to a gene chip in which none of the genes on the chip is a characterized gene. In general, gene chips are commercially successful and the skilled artisan would believe them to be useful. However, a gene chip would not meet the utility requirement if none of the genes on the chip had a specific and substantial utility.

In the 1/30/08 response, Applicants argue (pg 6) that the instant invention is a "pioneering invention" as described in *Westinghouse v. Boyden Power Brake Co* (1898).

Applicants' arguments have been fully considered but are not found persuasive. The fact pattern of the case cited by the Applicant and of the instant rejection are significantly different, and the court decision is not binding with regard to the instant rejection. In *Westinghouse*, the Supreme Court discussed the concept of a "pioneering invention" in regard to a consideration of the breadth of patented claims with respect to infringement by others. Significantly, there is no discussion in the decision of "pioneering inventions" with respect to rejections made under 35 U.S.C. § 101. Furthermore, the inventions described in *Westinghouse* ("fluid-pressure automatic-brake mechanism") had a specific and substantial utility in the braking of train cars.

In the 1/30/08 response, Applicants further argue (pg 7) that the claimed methods have utility analogous to that of polymerase chain reaction (PCR). Applicants

argue that "the utility of PCR is not derived from the identity of the polynucleotide being amplified, but rather from its ability to amplify virtually any polynucleotide of interest to a user regardless of its specific sequence or function" and "the utility of Applicants' claimed invention is derived not from the identity of the GPCR employed in the method, but rather from the ability of one to employ the claimed methods to identify modulating compounds for virtually any GPCR that is of interest". Applicants further argue that a user of the claimed invention "comes to the table with a GPCR of interest for which candidate modulatory compounds are sought".

Applicants' arguments have been fully considered but are not found persuasive. At the time of invention of PCR in 1983, many nucleic acid sequences existed that either had utility as markers or to encode specific proteins with utility. Thus, at the time of invention, PCR had immediate utility in producing large quantities of identical copies of nucleic acids with specific and substantial utility. In contrast, the instantly claimed methods are limited solely to identifying non-endogenous modulators of "orphan GPCRs". There is no specific and substantial utility for any of the non-endogenous compounds identified by the claimed methods. Further research would be required to identify a use for any of the modulators identified by the claimed methods.

In the 1/30/08 response, Applicants further argue (pg 7) that U.S. Patent 5,462,856 (Exhibit A with the 1/30/08 response) provides an "example from the GPCR screening field of patented claims that are not limited to a particular GPCR".

Applicants' arguments have been fully considered but are not found persuasive. The claims in the '856 patent are not limited to a method of screening with an "orphan GPCR", but instead are directed to a method of screening for an agonist or antagonist of any "GPC receptor" (GPCR). At the time of invention, there existed a number of GPCRs with specific and substantial utility that could be used in the claimed method and thus provided the claimed method with immediate real-world utility. For example, in working examples 1-5 taught by the '856 patent (col 15-17), the method of screening is used to identify agonists and/or antagonists of the beta 2-adrenergic receptor (Examples 1 and 2), α2 adrenergic receptor (Examples 3 and 4) or the serotonin receptor (Examples 5). The ligand and activity of each of these GPCRs was known. In

contrast, the claimed method is not directed to GPCRs in general, but is instead limited to orphan GPCRs that have no known ligand and which have no known activity that can be modulated for a useful purpose. Furthermore, it is noted that the '856 patent issued on 10/31/05, which is prior to the publication of the revised Utility Examination Guidelines 1/5/01 in the Federal Register.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 45-52, 61, 62, 69, 77, 79 and 80 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation. This rejection was set forth previously and maintained at pg 6-7 of the 6/13/07 Office Action for claims 34, 45-52, 61, 62 and 69; new claims 77, 79 and 80 are herewith included in this rejection.

Applicants' arguments (11/13/07, pg 7 and 1/30/08, pg 8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In each response, Applicants submit that the rejection of the claims for lack of utility "has been adequately addressed in the discussion in the preceding section of this response" (i.e., Applicants' response to the rejection under 35 U.S.C. § 101).

Applicants' arguments have been fully considered but are not found persuasive. For the reasons described above in the section "Claim Rejections – 35 USC § 101", the claimed invention is not supported by a specific and substantial asserted utility, and therefore it is maintained that one of skill would not know how to use the claimed invention without undue experimentation.

New rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34, 45, 48, 61, 77 and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Eggerickx et al, 1995. Biochem J. 309(Pt 3): 837-843; cited by Applicants on the IDS filed 10/2/98.

Claim 77 is addressed first as it is an independent claim from which the other claims depend.

The recitation of “for directly identifying a non-endogenous compound with compound efficacy as to an endogenous orphan GPCR” in the preamble of claim 77 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed process over one from the prior art. Therefore, the claimed process encompasses any method with the recited steps.

Eggerickx teaches "[a] human gene encoding an orphan G-protein-coupled receptor named ACCA (adenylate cyclase constitutive activator)" (Abstract, pg 837). Eggerickx teaches "In order to test for potential ligands, the coding sequence of this human orphan receptor gene was inserted in the expression vector pSVL and stably transfected CHO cell lines were established ... A number of potential ligands (including the cannabinoid agonists CP55940 and anandamide) were tested for their ability to stimulate or inhibit intracellular cyclic AMP accumulation, or stimulate InsP3 accumulation. None of the tested ligands was able to modify significantly the basal levels of either cyclic AMP or INSP3 in this stably transfected cell line. However, it was reproducibly observed that the basal intracellular cyclic AMP levels of the hACCA expressing CHO-K1 cell line was greatly increased in comparison with the wild-type CHO-K1 cells or stable CHO-K1 cells lines transfected with the pSVL vector alone, or with other G protein-coupled receptors". Thus, Eggerickx teaches a method of

subjecting an endogenous orphan GPCR (i.e., ACCA) to constitutive receptor activation to create a constitutively activated orphan GPCR (i.e., by expressing it in CHO cells), contacting said GPCR with a non-endogenous compound (e.g., CP55940, which is a non-endogenous compound) and comparing functionality in the presence and absence of the non-endogenous compound (Eggerickx compared the activity to basal levels). Step (d) is a mental identification that is contingent on the alteration of the GPCR functional activity by the test compound; the corollary inherent in this identification is that if the presence of the test compound does not measurably alter the functionality of the GPCR, the compound is not identified as having "compound efficacy". Furthermore, it is clear from the teachings of Eggerickx that if CP55940 had altered functionality of the GPCR, it would have been identified as a ligand and me the definition of having "compound efficacy" as used on page 18 of the instant specification. Therefore, these teachings of Eggerickx anticipate claim 77.

Claim 79 depends from claim 77 and limits the compared functionality to the GPCR to "binding to GTP". This limitation broadly encompasses indirect measurements of GTP binding, including measurements of cyclic AMP accumulation that reflects the amount of activated GPCRs binding to G proteins and binding GTP. Therefore, the teachings of Eggerickx described above also anticipate claim 79.

Claim 34 depends from claim 77 and limits the method such that the "compound is determined to be a compound that reduces the activity receptor state of said constitutively activated GPCR". As with part (d) of claim 77, this limitation is a mental identification that is inherent in the teachings of Eggerickx. Therefore, the teachings of Eggerickx described above also anticipate claim 34.

Claim 45 depends from claim 77 and limits the GPCR to one with a third intracellular loop comprising the sequence X1BBHyX2, wherein X1 and X2 can be any amino acid, B is a basic amino acid and Hy is hydrophobic amino acid. As shown in Figure 1 of Eggerickx (pg 839), the third intracellular loop of ACCA contains two sequences that meet this limitation, including 'CRHAQ' and 'QRHLL'. Therefore, the teachings of Eggerickx described above also anticipate claim 45.

Claim 48 depends from claim 45 and limits Hy to alanine. The sequence 'CRHAQ' contains alanine at the Hy position; therefore, the teachings of Eggerickx described above also anticipate claim 48.

Claim 61 depends from claim 45 and limits the X1BBHyX2 sequence to an endogenous sequence. The sequence of ACCA shown in Figure 1 is a native human sequence; therefore, the teachings of Eggerickx described above also anticipate claim 61.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646